Maine Center for Disease Control and Prevention
An Office of the Department of Health and Human Services
John E. Baldacci, Governor Brenda M. Harvey, Commissioner

Department of Health and Human Services
Maine Center for Disease Control and Prevention
286 Water Street
11 State House Station
Augusta, Maine 04333-0011
Tel: (207) 287-8016
Fax: (207) 287-9058; TTY: 1-800-606-0215

June 29, 2010

Commissioner David Littell
Maine Department of Environmental Protection
17 State House Station
Augusta, ME 04333

Dear Commissioner Littell:

38 MRSA §1694 requires that the designation of a "priority chemical" under Maine's Toxic Chemicals in Children's Products law be made in concurrence with the Department of Health and Human Services, Maine Center for Disease Control and Prevention (ME-CDC). By this letter and accompanying document, ME-CDC is informing the Department of Environmental Protection (ME-DEP) of its concurrence with its proposed designation of Nonylphenol and Nonylphenol Ethoxylates as priority chemicals.

Under 38 MRSA §1694, the ME-DEP may designate a chemical as a priority chemical if the Commissioner finds any of the following:

A. The chemical has been found through biomonitoring to be present in human blood, including umbilical cord blood, breast milk, urine or other bodily tissues or fluids;
B. The chemical has been found through sampling and analysis to be present in household dust, indoor air, drinking water or elsewhere in the home environment;
C. The chemical has been found through monitoring to be present in fish, wildlife or the natural environment;
D. The chemical is present in a consumer product used or present in the home;
E. The chemical has been identified as a high production volume chemical by the federal Environmental Protection Agency; or
F. The sale or use of the chemical or a product containing the chemical has been banned in another state within the United States.

ME-CDC's toxicologist, Dr. Deborah Rice, has reviewed ME-DEP's basis statement for designating Nonylphenol and Nonylphenol Ethoxylates as priority chemicals as well as a review of relevant scientific literature, and prepared the attached document providing our Agency's justification for concurrence based on evidence that these chemicals meet the criteria A – D above.

Sincerely,

Dora Anne Mills

Dora Anne Mills, M.D., M.P.H.
State Health Officer and Director,
Maine Center for Disease Control and Prevention

cc: Andrew E. Smith, SM, ScD, State Toxicologist, ME-CDC

Rationale for Concurrence by Maine Center for Disease Control and Prevention on the Designation of Nonylphenol and Nonylphenol Ethoxylates as a Priority Chemical

Prepared by Deborah Rice, PhD, Toxicologist

Maine Center for Disease Control and Prevention

June 29, 2010

Background

Under 38 MRSA §1694, the Commissioner of the Maine Department of Environmental Protection (ME-DEP) may designate a *chemical of high concern* as a *priority chemical* if the Commissioner finds any of the following:

A. The chemical has been found through biomonitoring to be present in human blood, including umbilical cord blood, breast milk, urine or other bodily tissues or fluids;

B. The chemical has been found through sampling and analysis to be present in household dust, indoor air, drinking water or elsewhere in the home environment;

C. The chemical has been found through monitoring to be present in fish, wildlife or the natural environment;

D. The chemical is present in a consumer product used or present in the home;

E. The chemical has been identified as a high production volume chemical by the federal Environmental Protection Agency; or

F. The sale or use of the chemical or a product containing the chemical has been banned in another state within the United States.

Once a chemical is listed as a priority chemical, the ME-DEP may require disclosure of information about the presence of the chemical in children's products (§1695) and prohibit sales of children's products including this chemical (§1696).

38 MRSA §1694 requires that the designation of a chemical as a *priority* chemical be made in concurrence with the Department of Health and Human Services, Maine Center for Disease Control and Prevention (ME-CDC).

The ME-DEP has proposed to list the chemicals *nonylphenol and nonylphenol ethoxylates* as a priority chemical. The Agency has requested that ME-CDC review the Department's draft *Basis Statement for Chapter 883 Designation of Nonylphenol and Nonylphenol Ethoxylates as a*

Priority Chemical and Safer Chemical Program Support Document for the Designation as a Priority Chemical of Nonylphenol and Nonylphenol Ethoxylates. [1]

ME-CDC concurs that it is appropriate to designate nonylphenol (NP) and nonylphenol ethoxylates (NPE) as a priority chemical under 38 MRSA §1694. In reaching its decision, ME-CDC performed its own review of the scientific literature relevant to findings under 38 MRSA §1694 (A), (B), (C), and (D), which are content areas within the expertise of the ME-CDC. ME-CDC also reviewed the evidence that NP, a degradation product of NPE, is an endocrine disruptor and a reproductive and developmental toxicant, which are criteria for designating a *chemical of high concern.* Since chemicals may be classified as of *high concern* for reasons other than human health hazard (i.e., persistent and bioaccumulative), ME-CDC viewed it appropriate to briefly review the toxicity data as well.

Overview of the chemical class nonylphenol and nonylphenol ethoxylates

NP are widely used for the synthesis of NPE, nonionic surfactants with a worldwide annual production in the hundreds of thousands of tons. NP are also used in the manufacture of plastics such as polystyrene and polyvinyl chloride, as inert ingredients in pesticides, and may be present in rubber and resins. The major source of NP in the environment is the microbial degradation of NPE, and NP have been detected in river water, sewage sludge, and drinking water (Ye *et al.*, 2007).

NP are a class of chemicals having a phenol ring attached to nine carbon atoms. The chain may be attached to the ring in one of three positions: ortho (*o* or 2); meta (*m* or 3); or para (*p* or 4). The alkyl chain can be a linear (*n*-) chain, or a complex branched chain. The commercial product is a mix of isomers, predominantly branched alkyl chain isomers of 4-NP, 4-tert-NP (Ye *et al.*, 2007). As many as 100 isomers have been reported in various environmental media (Thiele *et al.*, 2004; Eganhouse *et al.*, 2009; Ieda *et al.*, 2005; Ruβ *et al.*, 2005).

The primary concern for these compounds is due to their ability to bind to the estrogen receptor and thereby mimic the effects of estrogen. In an *in vitro* assay for estrogenic activity in fish, both NP and NPE were active (Jobling and Sumpter, 1993). Of the isomers tested, the *para* (4)-substituted isomers were active, whereas the *ortho* (2) and *meta* (3) isomers were not. There is also evidence that various 4-NP branched-chain isomers have differential estrogenic activity (Saito *et al.*, 2007). Biodegradation of NPE results in shortening of the ethyxylate chain into more toxic ethoxylates and NP, although NPE is generally considered to be less toxic than NP (Bakke *et al.*, 2003).

Most research studies, described below, do not specify which form of NP is being studied. It is presumed that most used the mixed isomer commercial product; although a small number of studies used the linear *(n-)* form.

[1] Draft Basis Statement for Chapter 883 Designation of Nonylphenol and Nonylphenol Ethoxylates as a Priority Chemical and Safer Chemicals Program Support Document for the Designation as a Priority Chemical of Nonylphenol and Nonylphenol Ethoxylates. Maine Department of Environmental Protection, Bureau of Remediation and Waste Management, 21 April, 2010.

Evidence that nonylphenol may be classified as an endocrine disruptor and a developmental and reproductive toxicant

NP acts as an estrogenic chemical, binding to the estrogen receptor and producing estrogenic effects in *in vitro* systems in a number of mammalian and non-mammalian species and tissues (Soto *et al.*, 1991, 1995; Shelby *et al.*, 1996; Laws *et al.*, 2000; Kwack *et al.*, 2002; Blair *et al.*, 2000; Danzo, 1997; Bonefeld-Jorgensen *et al.*, 2007; Vivacqua *et al.*, 2003). The NPE degradation product 4-nonylphenoldiethoxylate also has estrogenic properties in standard *in vitro* systems (White *et al.*, 1994). NP also exhibits estrogenic effects on standard estrogenic assays in the whole animal, including effects on uterine weight, time to puberty, and cancer tissue (Laws *et al.*, 2000; Odum *et al.*, 1999; Kwack *et al.*, 2002; Watanabe *et al.*, 2004; Kim *et al.*, 2002).

Gestational exposure to NP produced effects on mammary gland development and changes in hormone receptor densities (Moon *et al.*, 2007). Female rats exposed to NP in the early postnatal period showed altered estrus cycles and abnormal reproductive function (Nagao *et al.*, 2000). Exposure to NP in pregnant rats produced changes in estrogen-specific mRNA and protein levels in dams and fetuses, and decreased estrogen receptor density in the fetus (Hong *et al.*, 2004). In a study in human first-trimester placental tissue, exposure of chorionic villous to very low levels of NP produced estrogen-mimicking effects, including trophoblast differentiation and cell apoptosis (programmed cell death) (Bechi *et al.*, 2006). NP was more active and for a longer period than estrogen itself. A follow-up study (Bechi *et al.*, 2010) found that NP interfered with secretion of specific cytokines, chemicals that play a critical role in pregnancy, particularly during development of the placenta and implantation of the conceptus. These results raise concern about the effects of exposure to NP on the maintenance of pregnancy.

NP affect reproductive function in males as well, affecting sperm production (Adeoya-Osiguwa *et al.*, 2003), testicular growth (Jobling *et al.*, 1996), epididymus weight and reproductive hormone levels (Han *et al.*, 2004; Wu *et al.*, 2010; Gong and Han, 2006) in adult animals. Epididymal weight was decreased in offspring of rats exposed to NP during gestation (Hossaini *et al.*, 2001), and rats exposed during the early postnatal period exhibited changes in gonadal structure (Nagao *et al.*, 2000). NP increased apoptosis in Sertoli cells, in conjunction with morphological changes and decreased cell viability (Gong *et al.*, 2009; Wang *et al.*, 2003). Exploration of the mechanisms of apoptosis by NP identified several possible pathways (Wu *et al.*, 2009; Gong *et al.*, 2009).

NP affects organ systems in addition to the reproductive system, including as a result of developmental exposure. NP has a direct effect on the immune system (lymphocytic proliferation) by mechanisms independent of the estrogen or progesterone receptors (Iwata *et al.*, 2004; Mao *et al.*, 2008). *In utero* and postnatal exposure to NP also produced immune effects (changes in splenic natural killer cells and splenocyte subpopulations), with no effects observed in the dams (Karrow *et al.*, 2004). NP also produced apoptosis in thymocytes by specific mechanisms (Yao *et al.*, 2006), providing further evidence for disruption of the immune system by NP.

Researchers have also explored the effects of NP on the developing nervous system. NP induces death of murine (rat or mouse) (Kudo *et* al., 2004; Mao *et al.*, 2008) and human (Kim *et* al.,

2006) stem cells via a specific apopototic mechanism, suggesting that NP may affect neurogenesis in the central nervous system. There is also evidence that developmental exposure to NP affects thyroid function. *In utero* exposure resulted in changes in circulating levels of thyroid hormone (T_3) and/or thyroid stimulating hormone (TSH) in both sexes, in addition to changes in levels of certain reproductive hormones (Nagao *et al.*, 2001). NP has also been demonstrated to affect enzymes (aromatase) and receptors (aryl hydrocarbon and pregnane X receptor) involved in the synthesis and regulation of a number of other hormones in addition to reproductive hormones (Masuyama *et al.*, 2000; Bonefeld-Jørgensen *et al.*, 2007).

Evidence that nonylphenol is present in human tissue (38 MRSA §1694-A)

A recent review identified 20 studies in which NP was measured in human tissue (Lopez-Espinosa *et al.*, 2009). NP was detected in 18 of the studies, including in breast milk and cord blood, and blood, urine, and adipose tissue of adults. Only one study was performed in occupationally-exposed individuals, with the other studies representing environmental exposure. NP was generally detected in 50-100% of samples. A study in the United States measured 4-*n*-nonylphenol, the linear chain NP isomer, in 394 urine samples of 394 individuals >= 6 years of age from NHANES III (Calafat *et al.*, 2005). NP was detected in 51% of samples. The authors state that the isomer they measured represents a small percentage of total NP in the commercial mixture; so the total NP present may have been underestimated. Studies in Japan and Italy found NP in 100% of breast milk samples, and four studies found NP present in 26-86% of cord blood samples. A study in Taiwan compared levels of NP in maternal and umbilical cord blood in maternal-fetal pairs; levels in the mothers' blood generally exceeded those in the infant (Chen *et al.*, 2008).

Evidence for exposure to nonylphenol and nonylphenol ethoxylates by infants and children (38 MRSA §1694-B, C, and D)

NP and NP compounds have been found to be present in human food, including fresh fruit and vegetables (Yang and Ding, 2005), corn cereals (Carabias-Martinez *et al.*, 2006), eggs and milk (Shao *et al.*, 2007), and baby food purees of fruit and meat (Li *et al.*, 2008). A study in Germany identified 4-NP in a variety of foods, including fish, milk, cheese, eggs, pasta, and fruits and vegetables (Guenther *et al.*, 2002). Levels did not apparently correlate with the fat content of the product. The pattern of 4-NP in the various foods was similar to that of the commercial mixture. The authors suggest that there are multiple sources of NPs in food, including use of NPs as pesticides and surfactants, and in packaging material. NP and NPE are found in fish (Tsuda *et al.*, 2000), including those in U.S. waters (Keith *et al.*, 2001; Kannan *et al.*, 2003). An Italian study reported that levels of NP in breast milk correlated with fish intake in the mothers (Ademollo *et al.*, 2008).

NP and NPE have been detected in indoor air and house dust in a majority of homes tested in the U.S (Rudel *et al.*, 2001, 2003). NP have been found in food packaging, including polystyrene, polyolifins, and polyesters, cellulose and cellulose esters, rubbers, and coated paper (Fernandes *et al.*, 2008) and rubber products (Ozaki and Baba, 2003). A review by Muncke (2009) reported NP in a variety of foods from a number of container types, presumably at least in part as a result of oxidation of the antioxidant additive trisnonylphenol phosphate.

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